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REVIEW ARTICLE

Management of Dementia-Related Psychosis, Agitation and Aggression: A Review of the Pharmacology and Clinical Effects of Potential Drug Candidates

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Abstract
Along with cognitive decline, 90% of patients with dementia experience behavioral and psychological symptoms of dementia, such as psychosis, aggression, agitation, and depression. Atypical antipsychotics are commonly prescribed off-label to manage certain symptoms, despite warnings from the regulatory agencies regarding the increased risk of mortality associated with their use in elderly patients. Moreover, these compounds display a limited clinical efficacy, mostly owing to the fact that they were developed to treat schizophrenia, a disease characterized by neurobiological deficits. Thus, to improve clinical efficacy, it has been suggested that patients with dementia should be treated with exclusively designed and developed drugs that interact with pharmacologically relevant targets. Within this context, numerous studies have suggested druggable targets that might achieve therapeutically acceptable pharmacological profiles. Based on this, several different drug candidates have been proposed that are being investigated in clinical trials for behavioral and psychological symptoms of dementia. We highlight the recent advances toward the development of therapeutic agents for dementia-related psychosis and agitation/aggression and discuss the relationship between the relevant biological targets and their etiology. In addition, we review the compounds that are in the early stage of development (discovery or preclinical phase) and those that are currently being investigated in clinical trials for dementia-related psychosis and agitation/aggression. We also discuss the mechanism of action of these compounds and their pharmacological utility in patients with dementia.

1 Introduction

While describing the first case report of dementia, Alois Alzheimer indicated that along with memory impairment, the patient demonstrated symptoms of psychosis [1, 2]. Currently, it is widely recognized that neuropsychiatric disturbances constitute an inherent component of Alzheimer's disease (AD) and its related dementias. These manifestations are referred to in the literature as "behavioral and psychological symptoms of dementia" (BPSD), which include psychosis, agitation, aggression, irritability, depression, and anxiety [3]. It is estimated that at least one or more behavioral symptoms will manifest in almost all patients with dementia in the course of their disease [4]. Behavioral and psychological symptoms of dementia can decrease the quality of patients' lives and are often cited as the main reason for referring patients with dementia to nursing homes or similar institutions [5].

Currently, a specifically approved pharmacotherapy for BPSD remains elusive. The most troublesome psychiatric events such as aggression and the remaining symptoms psychosis and agitation are addressed with atypical antipsychotics administered off-label [6]. However, the clinical efficacy of these drugs is unsatisfactory because a large percentage of patients do not respond or respond partially to the drugs [7]. Moreover, atypical antipsychotics are not actually recommended for elderly patients because they pose a risk of many side effects [8]. Elderly patients seem to be particularly sensitive to severe adverse reactions induced by atypical antipsychotics such as excessive sedation, orthostatic hypotension and related complications such as falls, extrapyramidal symptoms, cognitive slowing, cardiovascular

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Key Points

Current pharmacotherapy of dementia-related psychosis and agitation/aggression relies on the off-label administration of atypical antipsychotics, which have limited clinical efficacy and induce various adverse reactions.

Genetic studies have suggested several druggable targets that correspond with the etiology of dementia-related psychosis and agitation/aggression: serotonin 5-HT_{2A} and 5-HT_{1A} receptors, serotonin transporter, alpha-1 adrenoceptor, and dopamine D_1 and D_3 receptors.

Novel therapeutic approaches may benefit particularly from targeting the serotoninergic system with serotonin 5-HT_{2A} and 5-HT_{1A} ligands or serotonin transporter inhibitors, which are currently being investigated in phase III clinical trials.

Preclinical and clinical studies have suggested other relevant molecular targets that may result in therapeutically acceptable efficacy: cannabinoid receptors, metabotropic glutamate 2 receptors, muscarinic M_1/M_4 receptors, and glutamate N-methyl-D-aspartate receptors.

Blockade of M_1, alpha-2 adrenergic, and histamine H_1 receptors and the human ether-a-go-go-related gene channel should be avoided because elderly patients are particularly sensitive to adverse reactions induced by the drugs acting on these targets.

complications, and anticholinergic side effects [9]. Notably, the use of currently available antipsychotics in patients with dementia has been associated with an increased risk of death. Consequently, in April 2004, the US Food and Drug Administration (FDA) issued a black-box warning against the use of atypical antipsychotics in elderly patients [10, 11]. The American and British clinical guidelines [12–14] state that antipsychotics can be used only if the patient constitutes a threat to self or others and should be administered after evaluating the benefit/risk ratio of the treatment [15]. If the physician decides to prescribe antipsychotics, clinical guidelines recommend the exclusive usage of the following drugs: risperidone, olanzapine, quetiapine, and aripiprazole [12]. Nevertheless, several reviews in this subject emphasized that prior to treatment with antipsychotics, one should always consider that these drugs exert detrimental effects and provide limited efficacy [6, 7, 16].

The main explanation for the poor clinical performance of atypical antipsychotics in elderly patients is that these were approved specifically for the treatment of schizophrenia, which affects mostly younger adults with neurobiological deficits that are distinct from BPSD. Aging induces changes in the quality and quantity of neurotransmitters, which may account for the onset of behavioral symptoms in patients with dementia [17, 18]. Consequently, fluctuations of neurochemicals initiate changes in the expression of certain receptors that should be targeted with specific medications [19]. Thus, patients with dementia might benefit from drugs interacting with relevant molecular targets to maximize the clinical response.

In this regard, a plethora of experimental evidence has recently highlighted several druggable targets that are believed to achieve therapeutically acceptable pharmacological profiles for BPSD. Several different drug candidates are being investigated in clinical trials for BPSD, which hopefully will make the pharmacotherapy of BPSD a realistic prospect. In this review, we present the drug candidates being currently investigated in clinical trials for BPSD. We focus on the most troublesome symptoms, aggression, agitation, and psychosis, which require pharmacological intervention. We discuss their pharmacological profile in terms of privileged biological targets, and assess how they correspond with the molecular mechanisms underlying their pathology. We also provide information on the latest investigational compounds at the early stage of development (discovery or preclinical phase). (For a review of the treatment of depression in patients with dementia, the reader is referred elsewhere [20]).

2 Overview of Potential Druggable Targets for Pharmacological Treatment Matching the Etiology of Dementia-Related Psychosis and Agitation/Aggression

The etiology of dementia-related psychosis and agitation/aggression is very complex and is often a cluster of biological factors (anatomical and neurochemical changes) as well as psychological and social aspects (responses to stress, living arrangements [21]). Alzheimer's disease is the most common type of dementia, and the pathophysiology of this particular disease is related to the loss of neurons. Depending on the degree of neurodegeneration, the cerebral region involved, and consequently the extent of deficits in neurotransmitters, various psychiatric symptoms may appear [22]. For instance, psychosis has been associated with neurodegeneration in the frontal and mesotemporal areas of the brain [23], while depression has been linked to the degeneration of brainstem aminergic nuclei and a decrease in serotonergic neurotransmission [24]. Additionally, neuropathological changes that cause hypofunction of the cholinergic and serotonergic systems and hyperfunction of dopaminergic and noradrenergic transmission have been linked to agitation manifested by patients with dementia [22]. Alterations

in multiple neurotransmitter systems cause changes in the expression of specific receptors, which have a direct impact on the regular functioning of the central nervous system (CNS) [3, 18].

Numerous studies have revealed a close association between genetic polymorphisms and the onset of psychiatric symptoms in patients with dementia. Particularly, serotonin 5-HT_{2A} receptors (5-HT_{2A}R) are related to the etiopathology of dementia-related psychosis and aggression. For instance, in patients with dementia, 5-HT_{2A}R binding is decreased [25]. Additionally, reduced density of 5-HT_{2A}R in the prefrontal cortex [26] and the polymorphism of 5-HT_{2A}R have been associated with an increased risk of hallucinations and aggression [26, 27]. Moreover, the type of hallucinations observed in patients with Lewy body dementia (mainly visual) suggests the involvement of serotonin 5-HT_{2A}R [28]. In fact, these resemble the hallucinations induced by 5-HT_{2A}R agonists lysergic acid diethylamide and mescaline rather than those found in patients with schizophrenia, which tend to be mainly auditory [29–31]. Therefore, compounds that preferentially block 5-HT_{2A}R might be used to treat dementia-related psychosis or aggression.

Similarly, other molecular targets have been associated with the manifestation of psychiatric symptoms in patients with dementia. A genetic study showed that the polymorphism of the serotonin transporter (SERT) promoter region (L/L genotype) is correlated with aggressive behavior in patients with AD [32, 33]. Furthermore, decreased density of 5-HT_{1A}R in the cortex has been directly linked with the onset of aggressive behavior in patients with AD [34]. Furthermore, postmortem studies in patients with AD indicated that neurodegeneration of noradrenergic neurons may account for the pathophysiology of agitation and aggression related to AD [35]. In addition, polymorphisms in dopamine D_1 receptor (D_1R) and D_3 receptors (D_3R) have been associated with dementia-related psychosis and aggression [36]. In summary, potential druggable targets that closely correspond with the pathology of dementia-related psychosis, agitation, and aggression include serotonin 5-HT_{2A}R and 5-HT_{1A}R, SERT, alpha-1 adrenoceptors, and D_1R and D_3R.

Preclinical studies disclosed another palette of interesting molecular targets that may exhibit therapeutically relevant pharmacological profiles. For instance, an experimental study showed that knockout mice deficient in the cannabinoid CB_1 receptor (CB_1R) displayed aggressive behavior, which could be reduced by the short-term administration of a CB_1R agonist [37]. Clinical evidence showed that the cortical areas in patients with AD are characterized by reduced expression and decreased availability of CB_1R [38]. Therefore, pharmacological modulation of CB_1R deserves a broadened evaluation to consider it as a potential molecular target in the management of AD-related aggression [39]. Furthermore, many findings suggest that neurodegeneration induces changes in the expression and function of metabotropic glutamate receptors (mGluRs) and *N*-methyl-D-aspartate (NMDA) receptors [40]. Disrupted glutamatergic neurotransmission, in turn, is a well-recognized factor that contributes to the pathophysiology of neuropsychiatric disorders [41, 42]. Studies in animal models revealed that the activation of metabotropic glutamate 2 receptor (mGlu2R) resulted in antipsychotic, memory-enhancing [43], and neuroprotective activity [44], while modulation of NMDA receptors is crucial for neuroplasticity and also influences mood and behavior [40]. Therefore, while developing drugs for dementia-related psychosis in the future, those targeting mGluRs or NMDA receptors can be considered as potential pharmacological targets. Furthermore, pharmacological activation of muscarinic receptors M_1/M_4 (M_1R/M_4R) may represent a disease-modifying [45] and symptomatic treatment [46]. Stimulation of M_1R/M_4R mediates key effects on cognitive performance, protects neurons from beta-amyloid toxicity [45], and promotes antipsychotic activity [46]. In addition, mounting evidence shows that patients with dementia may benefit from drugs targeting serotonin 5-HT_6 receptors (5-HT_6R) [47]. Preclinical studies revealed that selective 5-HT_6R antagonists display promising procognitive activity, as well as mood-modulating properties [48]. A summary of the potential molecular targets for the treatment of dementia-related psychosis and agitation/aggression is presented in Table 1.

3 New Drug Candidates on the Horizon

3.1 Identification of Compounds Investigated in Preclinical and Clinical Trials

To collect data regarding the compounds being investigated in clinical trials, we searched for trials registered by the US National Institutes of Health (http://www.clinicaltrials.gov) and EudraCT (https://eudract.ema.europa.eu) using the following keywords: "dementia" or "Alzheimer's disease" and/or "agitation," and/or "aggression" and/or "psychosis." We restricted the search for trials from 2014 to present to obtain the most recent overview covering the last 5 years. Additionally, we searched for literature data associated with the identified compounds, published from 2014 to the present, using the compounds' name and other keywords such as "Alzheimer's disease" and "dementia" or "aggression" or "psychosis." We used PubMed, ScienceDirect, GlobalData, and Google Scholar databases. If data regarding a compound's efficacy or the current status of its trial were not published or posted on clinical trial registries, we searched the websites of the pharmaceutical and biotech companies responsible for that compound's development. The search was restricted to English.

Table 1 Summary of the potential druggable targets that might be suitable for pharmacological modulation of selected behavioral and psychological symptoms of dementia (BPSD): psychosis, aggression, and agitation

Matching with BPSD pathology		Indicated by experimental studies	
Target	Pharmacological activity	Target	Pharmacological activity
Serotonin 5-HT_{2A} receptors	Antipsychotic, antiaggressive	Muscarinic M_1/M_2 receptors	Antipsychotic, procognitive
Serotonin 5-HT_{1A} receptors	Antiaggressive	Cannabinoid receptor CB_1	Antiaggressive
Serotonin transporter	Antiaggressive	Metabotrophic glutamate 2 receptor (mGlu2)	Antipsychotic
Dopamine D_1, D_2 receptors	Antipsychotic, antiaggressive	Serotonin 5-HT_6 receptors	Procognitive, anxiolytic
Alpha-1 adrenoreceptor	Antiaggressive		

The applied search resulted in the identification of several drug candidates being investigated in clinical trials. Table 2 summarizes the data extracted on the investigated drug candidates, which will be discussed in detail below (except for lithium, which has been reviewed comprehensively elsewhere [49, 50]).

4 Drug Candidates for Dementia-Related Psychosis and Agitation/Aggression in Clinical Trials

4.1 Drugs Affecting Serotonergic Neurotransmission

4.1.1 Serotonin 5-HT_{2A} Receptor Inverse Agonist: Pimavanserin

Among the various molecular targets considered as potential treatments of dementia-related psychosis or agitation/aggression, serotonin receptors have come into the limelight. Age-related decline in serotonin function has been linked with aggressive behavior in AD [77, 78]. Specifically, a reduced density and polymorphism of 5-HT_{2A}R have been observed with the onset of aggression and psychosis in patients with dementia [77]. Therefore, modulation of the activity of 5-HT_{2A}R seems to be a promising therapeutic strategy for reducing psychiatric symptoms that matches closely with the disease pathology.

A serotonin 5-HT_{2A}R inverse agonist, pimavanserin, has been proposed as a suitable agent for the treatment of dementia-related psychosis and agitation/aggression [79, 80]. Pimavanserin was the first antipsychotic agent approved by the FDA (in 2016) for the treatment of psychosis in patients with Parkinson's disease. It is a nondopaminergic, highly selective 5-HT_{2A} inverse agonist that acts predominantly on the 5-HT_{2A}R and, to a lesser degree, on another serotonin receptor subtype 5-HT_{2C} (Fig. 1) [81]. Pimavanserin displays no affinity to the other G protein-coupled receptors including dopaminergic, histaminergic, muscarinic, and adrenergic receptors [82]. Thus, it is believed that this compound does not induce adverse reactions that are characteristic of atypical antipsychotics. The unique pharmacological profile of pimavanserin is characterized by high affinity and specific functional activity at the 5-HT_{2A}R. As an inverse agonist, pimavanserin binds to the 5-HT_{2A}R and not only blocks its natural agonistic activity but also reduces its constitutive activity. Importantly, pimavanserin does not bind to striatal D_2 receptors, which indicates a high margin of safety in terms of the extrapyramidal side effects [83].

Preclinical studies revealed that pimavanserin reduced psychotic-like behavior in rodents [84, 85]. In clinical trials, pimavanserin was found to be effective in the treatment of delusions and hallucinations associated with Parkinson's disease [86]. These promising results encouraged the evaluation of the efficacy of this agent in other psychotic disorders, including AD-related psychosis. Recently, a phase II, randomized, double-blind, placebo-controlled study evaluated the efficacy of pimavanserin in patients with AD-related psychosis (NCT02035553) [57, 58]. In the study, 181 subjects with AD were enrolled and treated with pimavanserin (17 mg twice daily) for 12 weeks (Table 3). Pimavanserin showed a statistically superior effect to placebo (change in the psychosis score on Neuropsychiatric Inventory [NPI]-Nursing Home Version scale) and an acceptable tolerability profile with no undesirable side effects on cognition [58]. The sponsor (ACADIA Pharmaceuticals) is currently running a phase III study, 52-week, open-label extension study (registered in Europe:2017-004439-36) of pimavanserin in the treatment of psychotic symptoms and agitation in 750 patients with dementia [65].

As psychotic symptoms in patients with AD tend to remit and relapse [87], it has been suggested that it would be desirable to further evaluate the efficacy of pimavanserin in preventing psychotic symptoms in patients with AD. In this regard, a double-blind, placebo-controlled, phase III study (NCT03325556) is currently recruiting 356 participants to evaluate the efficacy of pimavanserin (34 mg once daily) in preventing the relapse of psychotic episodes in patients with dementia (primary outcome measure: time from

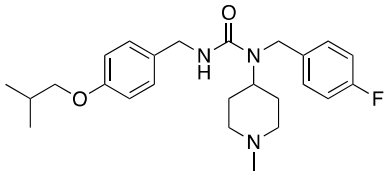
Table 2 Compounds investigated for the treatment of agitation, aggression, and psychosis associated with dementia of various types and their current status in clinical trials from 2014 to present

Compound	Identifier	Pharmacological action	Indication	Status	Estimated completion date
Compounds investigated in phase I					
HTL0016878	NCT03244228	Muscarinic M_4 agonist	Compound developed for: neurobehavioral symptoms in AD	Completed	September 2019 [51]
Compounds investigated in phase II					
Eltoprazine	H.134.5012 [52] GDCT0252614[a]	Serotonin 5-HT_{1A}/5-HT_{1B} partial agonist	Aggression associated with AD	Completed	December 2015 [52]
Lithium	NCT02129348	Complex	Psychosis, agitation in AD	Recruiting	January 2020 [50]
LY2979165 (MP-101)	NCT03044249	mGluR2 agonist	Psychosis, aggression, and agitation in dementia	Recruiting	August 2020 [53]
Prazosin	NCT03710642	Alpha-1 adrenoceptor antagonist [54]	Agitation in AD	Recruiting	December 2022 [55]
Pimavanserin	NCT03118947	Serotonin 5-HT_{2A}R inverse agonist	Agitation and aggression in AD	Completed	February 2019 [56]
Pimavanserin	NCT02035553	Serotonin 5-HT_{2A}R inverse agonist	Psychosis in AD	Completed	October 2016 [57, 58]
SND-51	GDC30016463[a] GDCT0310097[a]	DAAO inhibitor	Dementia and psychosis	Ongoing	Date has not been disclosed
Compounds investigated in phase III					
Nabilone	NCT02351882	Cannabinoid receptor (CB_1)	Agitation in AD	Completed	March 2019 [59–61]
AXS-05 (dextromethorphan/bupropion)	NCT03226522	Multi-receptor	Agitation in AD	Recruiting	June 2020 [62, 63]
Pimavanserin	NCT03325556	Serotonin 5-HT_{2A}R inverse agonist	Dementia-related psychosis	Recruiting	March 2020 [64]
Pimavanserin	2017-004439-36	Serotonin 5-HT_{2A}R inverse agonist	Neuropsychiatric symptoms related to neurodegenerative disease	Ongoing	Date has not been disclosed [65]
Pimavanserin	2017-002227-13	Serotonin 5-HT_{2A}R inverse agonist	Dementia-related psychosis	Ongoing	Date has not been disclosed [66]
Escitalopram	NCT03108846	SERT inhibitor	Agitation in AD	Recruiting	August 2022 [67]
Brexpiprazole	NCT03724942	Partial agonistic activity at dopamine D_2 and serotonin 5-HT_{1A}R, and antagonism of serotonin 5-HT_{2A}R [68]	Agitation in AD	Recruiting	May 2021 [69]
Brexpiprazole	2017-003940-19	Partial agonistic activity at dopamine D_2 and serotonin 5-HT_{1A}R, and antagonism of serotonin 5-HT_{2A}R [68]	Agitation in AD	Ongoing	Date has not been disclosed [70]
Brexpiprazole	2018-002783-88	Partial agonistic activity at dopamine D_2 and serotonin 5-HT_{1A}R, and antagonism of serotonin 5-HT_{2A}R [68]	Agitation in AD	Ongoing	Date has not been disclosed [71]
Lumateperone	NCT02817906	Antagonistic activity at the serotonin 5-HT_{2A} receptor, partial agonistic activity at the presynaptic dopamine D_2 receptor, antagonistic activity at the postsynaptic dopamine D_2 receptor [72], and SERT blockade	Agitation in dementia, including AD	Terminated	December 2018 [73]

Table 2 (continued)

Compound	Identifier	Pharmacological action	Indication	Status	Estimated completion date
AVP-923 (dextromethorphan/quinidine)	NCT02446132	Multi-receptor	Agitation in AD	Recruiting	June 2022 [74]
Mirtazapine	NCT03031184	Noradrenergic and specific serotonergic antidepressant	Agitation in dementia	Recruiting	July 2020 [75]
Compounds investigated in phase IV					
Gabapentin	NCT03082755	Calcium channel inhibitor	Night-time agitation and sleep disturbance in dementia	Recruiting	March 2022 [76]

AD Alzheimer's disease, *DAAO* D-amino acid oxidase, *mGluR2* metabotropic glutamate 2 receptor, *SERT* serotonin transporter
[a]GDCT trial identifier provided by GlobalData



Pimavanserin

5-HT_{2A} K_i = 0.4 nM
5-HT_{2C} K_i = 16 nM

Fig. 1 Structure and receptor profile of pimavanserin [81]

randomization to relapse in the double-blind period, up to 26 weeks) [62]. In parallel, the sponsor is running a phase III study registered in Europe (2017-002227-13), which evaluates the efficacy of pimavanserin in relapse prevention of psychotic symptoms in 212 patients with dementia [66]. In addition, a phase II open-label study (NCT03118947) [64] has been completed recently. The study evaluated the safety and tolerability of pimavanserin (10 or 17 mg twice daily, primary outcome measure: treatment-emergent adverse events [Table 3]). The results have not been revealed yet.

4.1.2 Serotonin $5\text{-HT}_{1A/1B}$ Receptor Agonist: Eltoprazine

Previous findings revealed that aggressive behaviors in patients with AD directly correlate with a reduced density of 5-HT_{1A}R in the CNS [34]. Several clinical reports disclosed a significant reduction in agitation and aggression in patients with dementia after the administration of drugs acting via 5-HT_{1A}R: tandospirone [88] and buspirone [89]. Therefore, it has been suggested that modulation of the activity of 5-HT_{1A}R might be considered as a promising therapeutic strategy for the treatment of dementia-related agitation/aggression.

Eltoprazine was developed as an anti-aggressive agent [90–92]. It was reported that eltoprazine potently suppressed aggressive behavior in animal models without causing sedation [93, 94]. Eltoprazine is a 5-HT_{1A}/5-HT_{1B} partial agonist but also acts as a full agonist at 5-HT_{2C}R (Fig. 2) [96]. Its anti-aggressive properties most probably result from the reduction in serotonin release due to the activation of presynaptic 5-HT_{1A} and 5-HT_{1B} autoreceptors [97, 98]. Moreover, mixed 5-HT_{1A}/5-HT_{1B} partial agonism of eltoprazine is responsible for its highly effective inhibition of aggressive behavior [98].

In phase I of clinical trials, eltoprazine was found to be safe and well tolerated [97]. In a phase II study on the treatment of AD-related aggression, eltoprazine showed promising results [52]. This double-blind, randomized, placebo-controlled study found that eltoprazine (10 mg once daily for 4 weeks) significantly reduced aggressive behavior

Table 3 Summary of completed clinical trials evaluating drug candidates in psychosis, aggression, and agitation associated with dementia and Alzheimer's disease (AD)

Drug/indication	Trial identifier	Study design				Results
		Participants	Dosing paradigm	Study design	Primary outcome measure	
Pimavanserin/psychosis in AD	NCT02035553 [57]	181 patients with AD	34 mg/day for 12 weeks	Phase II, single-center, double-blind, placebo-controlled	Change from baseline to week 6 in the NPI-NH psychosis score	Statistically superior effect of pimavanserin compared with placebo at the primary endpoint (week 6), with an acceptable tolerability profile and no negative effect on cognition (week 12) [58]
Pimavanserin/agitation and aggression in AD	NCT03118947 [56]	79 patients with AD	20 mg/day or 34 mg/day for 52 weeks	Phase II, open-label, single-group	TEAEs, safety and tolerability of pimavanserin after 52 weeks of treatment	Results not available yet
Eltoprazine/aggression in AD	H.134.5012 [52] GDCT0252614[a]	29 patients with SDAT or mixed SDAT/multi-infarct dementia	5–10 mg/day for 4 weeks	Phase II, multi-center, double-blind, randomized, placebo-controlled	Social Dysfunction and Aggression Scale and the Staff Observation Scale after 4 weeks	Significant improvement of aggressive behavior within the eltoprazine-treated group compared with the placebo group [52]
Citalopram/agitation in AD	NCT00898807 [191]	186 patients with AD	10–30 mg/day for > 3 weeks (based on response and tolerability)	Phase III, randomized, multi-center, placebo-controlled, double-blind	Evaluated by NBRS-A and mADCS-CGIC at week 9	Clinically meaningful reduction in the AD-associated agitation compared with placebo. [103] Cognitive and cardiac adverse effects associated with citalopram treatment
Escitalopram/psychotic symptoms and agitation in AD	NCT 01119638 [109]	40 patients with AD	Escitalopram/risperidone 5–10 mg/day and 0.5–1.0 mg/day for 6 weeks	Phase IV, randomized, double-blind, single-center, pilot	Change in the total score on NPI (week 6)	Escitalopram and risperidone were equally effective in reducing psychotic symptoms and agitation [110]
Mirtazapine/agitation in AD	Pilot study [176]	16 patients with AD	15–30 mg/day for 12 weeks	Open-label, prospective	Changes in behavior were assessed using CMAI-SF (2, 8, and 12 weeks)	Significant reduction in CMAI-SF and CGI-S between pre- and post-treatment with mirtazapine [176]. No significant side effect and cognitive deterioration

Table 3 (continued)

Drug/indication	Trial identifier	Study design				Results
		Participants	Dosing paradigm	Study design	Primary outcome measure	
Prazosin/agitation and aggression in AD	Pilot study [151]	22 patients with AD	Mean dose: 5.7 mg/day for 8 weeks	Double-blind, placebo-controlled, randomized	Improvement on BPRS and NPI at weeks 1, 2, 4, 6, and 8	Significant improvements in the NPI and BPRS within the prazosin-treated group compared with the placebo group [151]
Brexpiprazole/agitation in AD	NCT01862640 [192]	433 patients with AD	1 and 2 mg/day for 12 weeks	Phase III, randomized, double-blind, placebo-controlled, multi-center	Change in the CMAI total score (baseline to week 12). The secondary outcome is the change in the CGI-S score	The improvements in the primary endpoint of CMAI for brexpiprazole 2 mg were statistically better than placebo and appeared more robust than the improvements on the key secondary endpoint of CGI-S [114]
Brexpiprazole/agitation in AD	NCT01922258 [193]	270 patients with AD	A flexible dose range: 0.5 mg/day, 1 mg/day, or 2 mg/day for 12 weeks	Phase III, randomized, double-blind, placebo-controlled, multi-center	Change in the CMAI total score (baseline to week 12). The secondary outcome is the change in the CGI-S score	The improvements in the primary endpoint of CMAI appeared less robust than the improvements on the key secondary endpoint of CGI-S [114]
Lumateperone/agitation in AD	NCT02817906 [119]	177 patients with AD	9 mg/day for 4 weeks	Phase III, randomized, double-blind, placebo-controlled, multi-center	CMAI-C (week 4)	Terminated (pre-specified interim analysis indicated futility) [119]
THC/dementia-related neuropsychiatric symptoms (agitation, aggression, or aberrant motor behavior)	NCT01608217 [194]	50 patients diagnosed with AD, vascular dementia, or mixed dementia	4.5 mg/day for 3 weeks	Phase II, randomized, double-blind, placebo-controlled study, multi-center	NPI assessed at baseline and after 14 and 21 days	No significant difference in reduction from baseline between THC and placebo [163]
THC/dementia-related neuropsychiatric symptoms with at least agitation or aggression	NCT01302340 [195]	22 patients with AD, vascular dementia, or mixed dementia	Period A: 1.5 mg/day for 6 weeks Period B: 3 mg/day[b] for 6 weeks	Phase II, repeated crossover, randomized, double-blind, placebo-controlled, multi-center	Change in NPI score (at day 3 and 10 during treatment blocks and after 1 month)	No benefit of THC treatment (0.75 mg and 1.5 mg twice daily) on neuropsychiatric symptoms in dementia [164]
Dronabiol/dementia-related behavioral disturbances (aggression, agitation)	Retrospective study	40 patients with dementia	7.03 mg daily for 16 days	Retrospective	PAS (at day 7)	Total PAS score decreased significantly during dronabinol treatment [165]

Table 3 (continued)

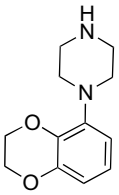
Drug/indication	Trial identifier	Study design				Results
		Participants	Dosing paradigm	Study design	Primary outcome measure	
Dronabiol/night-time agitation in dementia	Open-label pilot study	6 patients diagnosed with late-stage dementia (5 with AD, 1 with vascular dementia)	2.5 mg daily for 2 weeks	Open-label pilot	NPI, Actiwatch (at day 5)	Dronabinol led to a reduction in nocturnal motor activity [167]
Nabilone/agitation in AD	NCT02351882 [59]	39 patients with AD	1–2 mg for 14 weeks[c]	Phase II/III, pilot, randomized, double-blind, crossover	Change in agitation; CMAI (after 14 weeks)	Significant reduction in agitation over 6 weeks in the nabilone group. [60, 61] Sedation occurred during treatment with nabilone
AVP-923 (dextromethorphan/quinidine)/agitation in AD	NCT01584440 [196]	220 patients with AD	Dextromethorphan/quinidine at doses of 20 mg/10 mg once daily to 30 mg/10 mg twice daily for 10 weeks	Phase II randomized, multi-center, double-blind, placebo-controlled	Change from baseline in NPI Agitation/Aggression domain score (10 weeks)	Significant improvement on NPI, Agitation/Aggression score compared with placebo [128]

BPRS Brief Psychiatric Rating Scale, *CGI-S* Clinical Global Impression-Severity of Illness, *CMAI* Cohen-Mansfield Agitation Inventory, *CMAI-C* Cohen-Mansfield Agitation Inventory-Community, *CMAI-SF* Cohen-Mansfield Agitation Inventory-Short Form, *mADCS-CGIC* modified Alzheimer Disease Cooperative Study-Clinical Global Impression of Change, *NBRS-A* Neurobehavioral Rating Scale Agitation subscale, *NPI* Neuropsychiatric Inventory, *NPI-NH* Neuropsychiatric Inventory Nursing Home Version scale, *PAS* Pittsburgh Agitation Scale, *SDAT* senile dementia of Alzheimer's type, *TEAEs* treatment-emergent adverse events, *THC* Δ-9-tetrahydrocannabinol

[a]GDCT trial identifier provided by GlobalData

[b]Period A (6 weeks): 0.75 mg of THC twice daily for 3 successive days, separated by a 4-day washout. Period B: 1.5 mg of THC twice daily for 3 successive days, separated by a 4-day washout period

[c]14-week, randomized, double-blind, crossover trial compared nabilone to placebo (6 weeks each) with a 1-week washout between phases



Eltoprazine

5-HT$_{1A}$ K_i = 40 nM
5-HT$_{1B}$ K_i = 52 nM
5-HT$_{2C}$ K_i = 81 nM

Fig. 2 Structure and receptor profile of eltoprazine

(evaluated by the Social Dysfunction and Aggression Scale and the Staff Observation Scale) in 29 subjects (Table 3). These encouraging results suggest that further phase III clinical studies should be conducted on this indication.

4.1.3 Selective Serotonin Reuptake Inhibitors

Genetic studies revealed that certain forms of the SERT have been linked with the onset of dementia-related psychosis and aggressive behavior [32, 33]. In addition, administration of the selective serotonin reuptake inhibitor citalopram resulted in a significant decrease in the pathological levels of amyloid-β in patients with AD [99]. Preclinical studies have shown that citalopram blocked the growth of pre-existing amyloid-β plaques and reduced the formation of new plaques by 78% [100]. Moreover, selective serotonin reuptake inhibitors increase the levels of serotonin and thus may stimulate hippocampal neurogenesis [101]. Therefore, administration of the drugs acting on SERT to mitigate behavioral symptoms in patients with dementia is a rational intervention.

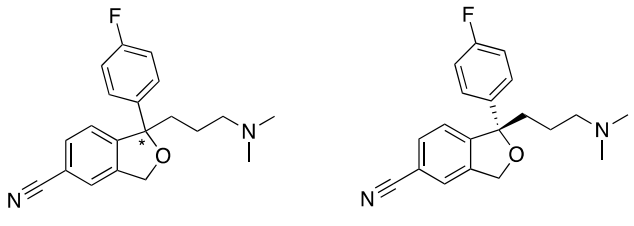
One of the first studies showed the effectiveness of citalopram in a short-term in-hospital management program of dementia-related aggression and agitation in patients with dementia [102]. These preliminary data have been confirmed in a larger randomized, placebo-controlled, double-blind study (NCT00898807) that enrolled 186 patients with AD [103] (Table 3). The study showed that long-term administration of citalopram (10–30 mg/day for 3 weeks) led to a clinically meaningful reduction in the AD-associated agitation compared with placebo (primary outcome measured by the Neurobehavioral Rating Scale Agitation subscale). However, treatment with citalopram has been associated with mild cognitive decline and cardiac side effects (QT interval prolongation), which hampers its long-term clinical application. In fact, in August 2011, the FDA announced a safety warning recommending to limit the maximum dose of citalopram to 20 mg/day in elderly patients aged > 60 years because of the possible occurrence of QT prolongation [104]. Therefore, it has been suggested that lower doses (< 30 mg/day) of citalopram [103] or alternatively other non-cardiotoxic antidepressants should be evaluated in clinical trials [105].

An (S)-stereoisomer of citalopram (Fig. 3), escitalopram, seems to be safer, as the magnitude of QT prolongation observed with this compound is lower compared with citalopram and the effect is dose dependent [106–108]. A randomized, double-blind, pilot study evaluated the effectiveness of escitalopram (5–10 mg/day) in reducing psychotic symptoms and agitation in 40 patients with AD in a 6-week treatment period (primary outcome measure: change in the total score on NPI), in comparison to the antipsychotic risperidone (0.5–1.0 mg/day) [109]. This study found that escitalopram and risperidone were equally effective (Table 3) [110]. The authors did not observe any adverse event in the escitalopram group. This pilot study justified the need for a larger, more comprehensive study. Currently, a phase III, double-blind, randomized, placebo-controlled trial (NCT03108846) [67] is recruiting patients with AD-related dementia and clinically significant agitation (392 participants) to evaluate the safety and effectiveness of escitalopram at a dose of 5–15 mg/day in reducing agitation in patients with AD during 12 weeks (primary outcome measure: change in the modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change score after 12 weeks) [67].

4.2 Drugs Acting on Several Biological Targets

4.2.1 Novel Atypical Antipsychotics

Recently, two novel atypical antipsychotic agents have been investigated in phase III clinical trials for AD-related agitation and psychosis: brexpiprazole and lumateperone. These agents target primarily the serotonin 5-HT$_{2A}$Rs while maintaining a relatively weaker interaction with D_2R, which makes them less likely to induce unfavorable extrapyramidal side effects. Elderly patients are particularly sensitive to extrapyramidal symptoms [111] owing to an aging-related impairment of dopamine function [112]; therefore, the interaction of these agents with the D_2R should be retained at the lowest level.



Citalopram

SERT K_i = 1.6 nM

Escitalopram

SERT K_i = 0.8 nM

Fig. 3 Chemical structure and binding profile of citalopram and escitalopram [107]. *SERT* serotonin transporter

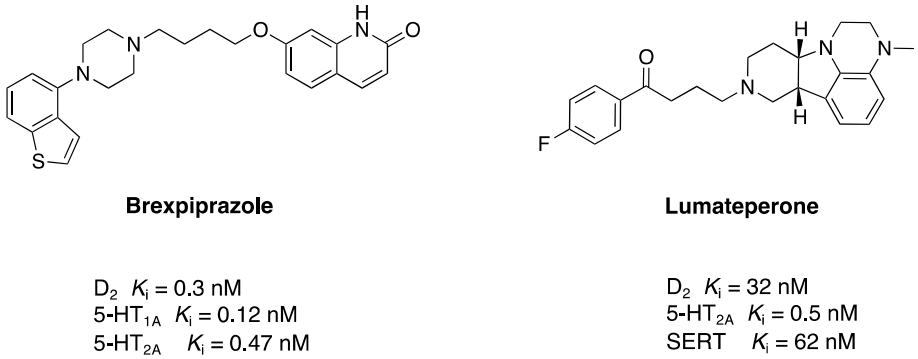


Fig. 4 Chemical structures and receptor profiles of brexpiprazole and lumateperone [68, 72]. *SERT* serotonin transporter

Brexpiprazole is a novel atypical antipsychotic approved by the FDA in 2015 for the treatment of schizophrenia and major depressive disorder as an add-on therapy [113]. Its mechanism of action is mediated via the antagonism of 5-HT_{2A}R and partial agonism of D_2R and 5-HT_{1A}R (Fig. 4) [68]. Partial agonistic activity at the D_2 receptor accounts for the reduced occurrence of extrapyramidal side effects. Lately, two phase III clinical trials have evaluated the safety and efficacy of brexpiprazole in AD-related agitation (NCT01862640 investigated two-fixed doses of 1 and 2 mg/day and NCT01922258 investigated the flexible dosing of 0.5, 1.0, or 2.0 mg/day during the 12-week treatment). These randomized, double-blind, placebo-controlled, multicenter studies enrolled 433 and 270 participants, respectively (Table 3). The sponsor announced that brexpiprazole significantly ameliorated the symptoms of agitation in comparison to placebo (evaluated by a change from baseline in the Cohen-Mansfield Agitation Inventory [CMAI] total score) [114, 115]. A corresponding trial (phase III, 12-week, multicenter, randomized, double-blind, placebo-controlled, two-arm, fixed-dose: 0.5 mg and 1 mg, 225 patients) registered in Europe (2017-003940-19) has not been accomplished yet [70]. In addition, a phase III, multi-center, active-treatment-extension trial (NCT03724942) is recruiting 250 patients to evaluate the safety and tolerability of brexpiprazole (2–3 mg/day for 12 weeks) in patients with AD-associated agitation (primary outcome data will include adverse events elicited from participants) [116]. A corresponding European active-treatment extension trial (a phase III, 12-week, multicenter study, 225 patients with dementia) is ongoing (2018-002783-88 [70]).

Lumateperone is another atypical antipsychotic drug with a mechanism of action based on the antagonistic activity at the 5-HT_{2A}R, partial agonistic activity at the presynaptic D_2 receptors, and antagonistic activity at the postsynaptic D_2R [72, 117], as well as SERT blockade (Fig. 4). Clinical studies in healthy volunteers using positron emission tomography revealed that lumateperone displayed high occupancy of the 5-HT_{2A}R in the cortex and negligible occupancy of the D_2 striatal receptors [118], suggesting that it is less likely to induce extrapyramidal side effects. Lumateperone has a unique mechanism of action, modulating synergistically multiple neurotransmitter systems, and has been suggested as a potential treatment for a range of neuropsychiatric disorders [73]. A recently completed phase III, randomized, double-blind, placebo-controlled, multi-center study (NCT02817906) has investigated the efficacy and safety of lumateperone (9 mg/day for 4 weeks; primary outcome measured using CMAI-Community Version) in 177 patients with dementia with clinically significant agitation (Table 3). The sponsor announced that the study was unlikely to meet its primary endpoint upon completion [119], and therefore, it has been terminated.

4.2.2 Dextromethorphan Formulations

Preclinical data revealed that a sigma-1 receptor agonist, dextromethorphan, exerts promising mood-modulating properties [121] For instance, dextromethorphan showed anti-stress activity by reducing fear stress in conditioned mice, which was suggested to involve a sigma-1-dependent stimulation of the dopaminergic system [121]. Further studies in rodents revealed that dextromethorphan displayed anti-depressive-like activity and exerted neuroprotective and antioxidant effects [122, 123]. Dextromethorphan is an FDA-approved antitussive drug that acts in the CNS [124, 125]. Dextromethorphan exhibits high affinity to several biological targets: sigma-1 receptor, SERT, norepinephrine transporter, NMDA receptor, alpha-2 adrenoceptor, histamine H_1 receptor (H_1R), and nicotinic α3β4 receptor (Fig. 5) [124].

The specific receptor profile of dextromethorphan contributes to its complex pharmacological activities, which prompted scientists to investigate its therapeutic potential in dementia-related agitation. However, dextromethorphan showed an unfavorable pharmacokinetic profile in humans, related to its rapid hepatic metabolism, which hampered the attainment of therapeutic concentrations in the brain. To reduce the first-pass effect and improve its pharmacokinetics, dextromethorphan was combined with a cytochrome P450 2D6 inhibitor, quinidine (formulation known as

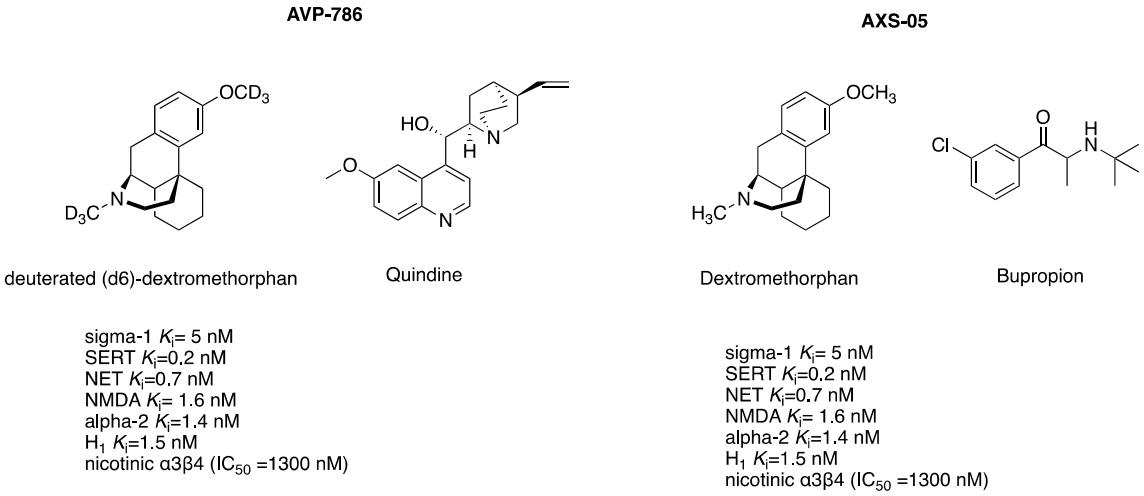


Fig. 5 Chemical structure of deuterated (d6) dextromethorphan/quinidine (AVP-786) and dextromethorphan/bupropion (AXS-05). *NET* noradrenaline transporter, *NMDA N*-methyl-D-aspartate, *SERT* serotonin transporter

AVP-923). Quinidine is an anti-arrhythmic agent used in clinical practice (200–300 mg) to treat cardiac arrhythmias [124, 126]. It reversibly inhibits cytochrome P450 2D6, and has been added to formulations at subclinical doses (10 mg) to inhibit cytochrome P450 2D6 and prolong the plasma half-life of dextromethorphan [124]. AVP-923 (Neudexta) has been approved by the FDA for the treatment of pseudobulbar affect [127].

The first clinical study, a phase II, randomized, multi-center, double-blind, placebo-controlled trial (NCT01584440), evaluated the efficacy of AVP-923 (dextromethorphan/quinidine at the doses of 20/10 mg once daily to 30/10 mg twice daily for 10 weeks) in reducing agitation in 220 patients with dementia, and revealed that AVP-923 exerted statistically significant effects on agitation compared with placebo (primary outcome measure was the change from baseline in the NPI Agitation/Aggression domain score) [128] (Table 3). Meanwhile, another formulation had been developed, containing a subclinical dose of quinidine and deuterated dextromethorphan (AVP-786). Dextromethorphan (Fig. 5) was deuterated to additionally improve its pharmacokinetic profile and reduce its first-pass metabolism in the liver [126]. Using the data generated for AVP-923, the FDA agreed to initiate a follow-up, phase III clinical trial (NCT02446132), an extension study, to evaluate the long-term safety and efficacy of AVP-786 (three various doses administered twice a day over 52 weeks) in the management of dementia-associated agitation [129]. The primary outcome measure includes, inter alia, the number of participants with any treatment-emergent serious adverse event, the Mini-Mental State Examination score, and the Alzheimer's Disease Assessment Scale-Cognitive Subscale score [74].

Based on the promising results of previous studies, experts strongly believe that AVP-786 may become the first FDA-approved deuterated compound for the treatment of dementia-related agitation [126]. However, it should be emphasized that the first dextromethorphan/quinidine formulation (AVP-923, Neudexta) label carries a warning regarding cardiac safety [127], suggesting that this compound should be avoided in patients with congenital long-QT syndrome and the QTc interval should be evaluated in the patients at risk of QTc prolongation [126, 127].

Another combination formula that includes dextromethorphan is AXS-05, which contains low doses of bupropion. Bupropion inhibits the reuptake of norepinephrine and dopamine and antagonizes nicotinic receptors. As a potent cytochrome P450 2D6 inhibitor, bupropion was added to the formulation to increase the plasma concentrations of dextromethorphan [130]. AXS-05 received a fast-track designation from the FDA for the evaluation of its efficacy in the treatment of AD-related agitation [131]. Currently, a phase II/III clinical trial (NCT03226522) [62] is evaluating the safety and efficacy of AXS-05 (one tablet daily for 5 weeks) for its use in the management of AD-related agitation (primary outcome measured using CMAI). This randomized, double-blind, placebo-controlled study enrolled 435 subjects with AD. Recently, the sponsor has announced the positive outcome of the interim analysis of the study and received recommendation for further continuation [63].

4.3 Drugs Affecting Glutamatergic Neurotransmission

4.3.1 Metabotropic Glutamate 2 Receptor Agonist: LY2812223

In the early 1990s, it was first proposed that dysfunction in glutamatergic neurotransmission could be implicated in

mental disorders [132]. Therefore, it was postulated that modulation of glutamatergic activity may constitute a novel nondopaminergic strategy for the treatment of psychosis [133–135]. Additionally, previous studies highlighted the activation of glutamate receptors exerts neuroprotective and memory-enhancing effects in animal models, which might be particularly beneficial to patients with dementia [42]. Eli Lilly and Company discovered LY2812223 (Fig. 6), a mGluR2 agonist [136, 137]. LY2812223 was found active in an animal model of psychosis, sensitive to mGluR2 [95, 137]. Unfortunately, in the pharmacokinetic studies, LY2812223 showed a poor oral bioavailability (~4%). However, this did not limit the further development of the mGluR2 agonist for the treatment of mental disorders. Low bioavailability of LY2812223 was overcome by designing its alanine prodrug MP-101 (LY2979165). MP-101 is administered orally and absorbed in the gastrointestinal tract through active transport and then, it is rapidly hydrolyzed to LY281223 (Fig. 6) [95, 138].

MP-101 is under development for the treatment of dementia-related psychosis and/or agitation and aggression (NCT03044249) [139]. This randomized, placebo-controlled, phase II clinical trial will assess the efficacy (measured as the change from baseline in the NPI-Psychosis subscale score), safety, and pharmacokinetic profile of MP-101 (20–60 mg/day for 10 weeks), compared to placebo. LY2979165 was previously evaluated in healthy subjects, in whom it was overall well tolerated and showed a linear pharmacokinetic profile [53, 137].

4.3.2 Inhibitors of D-Amino Acid Oxidase

An interesting approach for indirectly controlling the glutamatergic neurotransmission is to inhibit the activity of D-amino acid oxidase (DAAO). D-amino acid oxidase regulates the brain levels of D-amino acids, and in several psychiatric conditions, the activity and expression of DAAO are enhanced [140]. Overactivation of DAAO decreases the availability of D-serine, an endogenous agonist of the NMDA receptor. N-methyl-D-aspartate dysfunction in turn has been associated with schizophrenia and AD [141]. D-amino acid oxidase inhibitors were found to exert antipsychotic activity and improve cognitive function in AD [142, 143]. Currently, SyneuRx International Corp. is developing a competitive antagonist of DAAO, compound SND-51, for the treatment of dementia and psychosis. SND-51 is botanic in origin (chemical structure has not been disclosed), and in animal models, it elicited antipsychotic and anxiolytic activity and improved spatial memory [144]. SND-51 has now progressed to phase II clinical trials, and its efficacy in the treatment of dementia and psychosis is being evaluated [145].

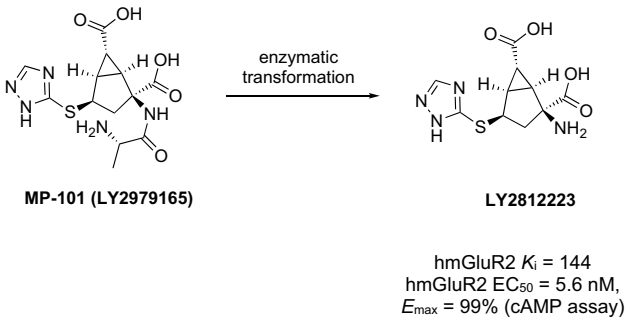


Fig. 6 Chemical structure and metabolic activation of MP-101, a prodrug of LY281223. *cAMP* cyclic adenosine monophosphate, *hmGluR2* human metabotropic glutamate receptor type 2

4.4 Drugs Affecting Cholinergic Neurotransmission

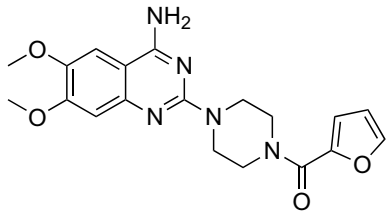
4.4.1 Selective Muscarinic M_4 Receptor Agonist: HTL0016878

Another promising example of compounds being developed for treating dementia-related psychosis and agitation/aggression is the selective muscarinic M_4R agonist HTL0016878 (chemical structure has not been disclosed). The muscarinic receptors are abundantly expressed in the cortex and hippocampus, the areas involved in cognitive and neurobehavioral functions [146]. In animal models, nonselective M_1R/M_4R agonists improved psychotic behaviors and cognitive performance [46]. These findings have been confirmed in muscarinic M_4R-knockout mice, and thus, it has been suggested that M_4R agonists represent an attractive molecular target for the development of novel antipsychotic agents [120]. A first-in-class selective M_4R agonist, HTL0016878, developed by Sosei Heptares for the treatment of neurobehavioral symptoms in patients with AD, has advanced to phase I clinical trials (NCT03244228). This randomized, double-blind, placebo-controlled study evaluated the safety, pharmacokinetics, and pharmacodynamics of this compound in 106 healthy young volunteers as well as in elderly patients [51]. The results have not been revealed yet.

4.5 Drugs Affecting Noradrenergic Neurotransmission

4.5.1 Alpha-1 Adrenoceptor Inhibitor: Prazosin

Several findings indicated the robust association between noradrenergic depletion and AD [35, 147, 148]. Postmortem studies revealed that the prefrontal cortex in patients with AD was characterized by a significant reduction in noradrenergic neurons [148], which may be associated with a poor cognitive performance as well as the onset of aggression [147]. Postmortem studies also showed that the



Prazosin

alpha 1A K_i = 0.01 nM

Fig. 7 Chemical structure and binding profile of prazosin [154, 155]

compensatory upregulation of postsynaptic alpha-1 adrenoceptor is linked with AD-related aggression [149, 150]. Therefore, it has been proposed that reducing the activity of the overstimulated postsynaptic alpha-1 adrenoceptors may alleviate the aggressive behavior [151, 152].

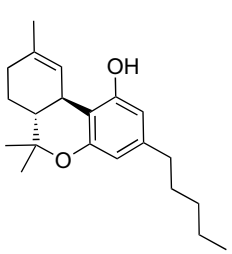
Among dugs acting on the alpha-1 adrenoceptors, prazosin remains the only centrally acting agent that can readily pass the blood–brain barrier and block the alpha-1 adrenoceptors in the CNS (Fig. 7) [153]. The first pilot study that evaluated the effectiveness of prazosin in suppressing the dementia-related aggression and agitation was a double-blind placebo-controlled study that enrolled 22 patients with AD [151] (Table 3). Administration of prazosin (mean dose: 5.7 mg/day, 8 weeks) led to a significant reduction in aggression/agitation (improvement on the Brief Psychiatric Rating Scale and the NPI score) compared with placebo [151]. Side effects and blood pressure fluctuations were comparable between the prazosin group and the placebo group. These data provided further support to initiate a larger phase II study (NCT03710642) enrolling 186 patients with AD with agitation [55]. This double-blind, placebo-controlled, randomized study will evaluate the effectiveness of prazosin (4–6 mg/day) in reducing agitation in patients with AD during 12 weeks (primary outcome measured using Clinical Global Impression of Change in Agitation) [55].

4.6 Drugs Targeting the Endocannabinoid System

Targeting cannabinoid receptors has acquired paramount importance as it offers a perspective to treat the symptomatology and pathology of AD [156]. Activation of cannabinoid receptors by agonists at non-psychoactive doses induces neuroprotective effects [157, 158] and can influence mood and behavior [156]. Preclinical studies have shown that cannabinoid receptor agonists decrease amyloid-β levels and reduce neuroinflammation [159, 160]. Further preclinical studies showed that a cannabinoid receptor agonist reduced aggressive behaviors [37, 161, 162]. These data suggest that cannabinoid receptor agonists may serve as a potential treatment for managing AD-related aggression.

Among the various cannabinoid receptor agonists, Δ-9-tetrahydrocannabinol (THC), dronabinol, and nabilone (Fig. 8) [synthetic analogs of THC] have been the most widely investigated in clinical trials [156]. A randomized, double-blind, placebo-controlled study that investigated the effect of THC (1.5 mg administered three times daily for 3 weeks) in 50 patients with dementia agitation or aggression found no significant differences between the treatment group and the placebo group (primary outcome measured using the NPI) [163]. Similarly, another trial showed no efficacy for THC in reducing agitation or aggression [164] (Table 3).

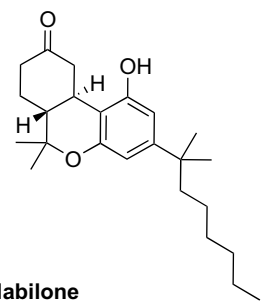
In contrast, a synthetic analog of THC, dronabinol, was found to be effective in reducing agitation in patients with dementia [156]. A retrospective study conducted on 40 acutely hospitalized patients with severe dementia showed that dronabinol (7 mg/day for 2 weeks) significantly reduced motor agitation and aggressiveness (a significant decrease in all domains of the Pittsburgh Agitation Scale) [165]. However, some authors reported the occurrence of adverse effects associated with dronabinol use, with a particular emphasis on sedation [165, 166]. Other studies found that dronabinol reduced night-time agitation [165, 167–169] in patients with dementia. An open-label pilot study of six patients with dementia with night-time agitation treated with dronabinol (2.5 mg/day for 2 weeks) reported a significant reduction in nocturnal motor activity [167] (assessed using the NPI scale) (Table 3). These encouraging results led to further interest in this class of compounds and the initiation of a clinical investigation of another synthetic cannabinoid, nabilone. First, the efficacy of nabilone has been only described in two case reports, which described the improvement of behavioral disturbances (agitation and psychosis) in patients with dementia after treatment with nabilone [170, 171]. Further, a



Dronabinol

CB_1 K_i = 40 nM

CB_2 K_i = 36 nM

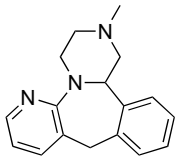


Nabilone

CB_1 K_i = 2.2 nM

CB_2 K_i = 1.8 nM

Fig. 8 Chemical structure and receptor affinity of dronabinol and nabilone [160, 161]. *CB* cannabinoid



Mirtazapine

5-HT_{2A}	K_i = 6.3 nM
5-HT3	K_i = 2900 nM
alpha 2A	K_i = 20 nM
alpha 2B	K_i = 88 nM
alpha 2C	K_i = 18 nM
H_1	K_i = 1.6 nM

Fig. 9 Chemical structure and binding profile of mirtazapine [180]

randomized, double-blind, placebo-controlled cross-over trial (NCT02351882) [59] evaluated the safety and effectiveness of nabilone (1–2 mg) for 14 weeks (6-week treatment with a 1-week washout between phases) in the management of agitation in 39 patients with AD (primary outcome measured using CMAI) (Table 3). The authors reported a statistically significant reduction in agitation within the nabilone group [60, 61]. During the treatment, the patients treated with nabilone experienced sedation. The authors concluded that nabilone may constitute a promising treatment for agitation associated with AD; however, the obtained data should be confirmed in a longer and larger study and side effects such as sedation and possibly cognitive decline should be monitored [61]. Nevertheless, nabilone seems to have a greater effect in reducing agitation, compared with other cannabinoids such as THC and dronabinol [61] and offered the most favorable pharmacokinetic profile among all the studied cannabinoids [172]. Further clinical studies are warranted to confirm its efficacy.

4.7 Drugs Improving Sleep Quality Displaying Various Mechanisms of Action

4.7.1 Noradrenergic and Specific Serotonergic Antidepressant: Mirtazapine

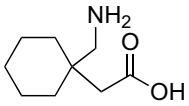
Nocturnal sleep quality may contribute to the onset of behavioral problems in patients with dementia [173]. Clinical observations suggested that agitative behavior in patients with dementia might be caused by sleep disturbances [174, 175]. In this regard, it has been proposed that both conditions could be effectively addressed by a drug that displays anxiolytic as well as sleep-promoting activity [176].

Mirtazapine is an antidepressant with sedative properties and an ability to promote sleep [177, 178]. It interacts with several types and subtypes of receptors including serotonin 5-HT_{2A}R and 5-HT_3R, alpha-2 adrenoceptors, and H_1R (Fig. 9) [179]. The unique pattern of receptor modulation by mirtazapine not only ameliorates psychiatric symptoms but also helps to improve sleep quality [178]. The first pilot study evaluating the effect of mirtazapine (15–30 mg/day) on AD-related agitation was a 12-week open-label, prospective study that included 16 patients who had clinically significant agitation [176] (Table 3). The authors observed a significant reduction in agitation in the patients treated with mirtazapine compared with pre-treatment with mirtazapine (changes in behavior were assessed using CMAI-Short Form) [176]. These encouraging data prompted the initiation of a larger phase III, pragmatic, multi-center, double-blind, placebo-controlled, randomized study (NCT03031184), which is currently recruiting 222 patients to evaluate the safety and effectiveness of mirtazapine (15–30 mg/day for 12 weeks) in reducing AD-related agitation (primary outcome measure: CMAI score at 12 weeks) [75].

4.8 α2δ Subunit-Containing Voltage-Dependent Calcium Channel Blocker: Gabapentin

In a large percentage of patients with dementia, agitation and wandering manifest during the night-time [173]. The nocturnal episodes of behavioral disturbances have a negative influence on daily functioning and additionally induce aggression during the day [173]. This vicious circle might be broken by treatment with a sedative agent that can help to decrease agitation and improve sleep quality during the night.

In 2011, a case report described the effectiveness of gabapentin in reducing the dementia-associated nocturnal agitation [181]. Gabapentin is an FDA-approved drug for the treatment of epilepsy [182]. Gabapentin blocks the α2δ subunit-containing voltage-dependent calcium channels (Fig. 10), which are associated with the release of neurotransmitters [183, 184]. Gabapentin displays a versatile pharmacological profile, including anticonvulsant, sedating, and anxiolytic activities [185]. In addition, the positive effects of gabapentin on the sleep quality and architecture have been well documented [186]. A series of case reports have described the treatment of patients with dementia with agitation using gabapentin and showed that the patients responded to the treatment favorably [187, 188]. Currently, gabapentin is being investigated in a phase IV study (NCT03082755) to test its effect (300–600 mg/day) on night-time agitation (primary outcome measure: night-time agitation measured using CMAI) [119]. During the 8-week treatment, this double-blind, placebo-controlled, randomized clinical trial will enroll 136 participants [76]. The remaining options available for the treatment of sleep disturbances and nocturnal agitation such as benzodiazepines are not recommended in vulnerable elderly individuals because these agents are well documented to cause harmful effects such as cognitive worsening and increase the risk of fall-related injuries [189].



Gabapentin

$\alpha_2\delta$ VDCC K_i = 0.05 μM

Fig. 10 Chemical structure and binding profile of gabapentin [190]. *VDCC* voltage-dependent calcium channel

5 Compounds in the Early Stage of Development (Discovery or Preclinical Phase)

We additionally searched for literature data associated with the identified compounds in the early stage of development (discovery or preclinical phase), published from 2014 to the present day to obtain the most recent overview covering the last 5 years, using the compounds' name and other keywords such as "Alzheimer's disease" and "dementia" or "aggression" or "psychosis." We used PubMed, ScienceDirect, GlobalData, and Google Scholar databases for our search (papers written in English). If data regarding the identified compounds were not published, we searched the websites of pharmaceutical and biotech companies responsible for the compounds' development. Several molecules that matched the selection criteria were identified, which are described in detail below.

5.1 Multi-Target-Directed Ligand Concept

It has been suggested that parallel modulation of several molecular targets may result in a balanced, and thus superior, pharmacological action, compared to a selectively acting drug. Considering this, a novel approach in drug discovery involves designing a single chemical entity that can simultaneously modulate the activity of several biological targets. Such compounds are described in the literature as "multi-target-directed ligands" [197]. The multi-target-directed ligand concept intended to design "clean" ligands that bind to selected molecular targets while sparing off targets, and thus reduce the risk of side effects [198]. The multi-target-directed ligand concept is relatively new; however, it has recently been widely explored in the literature and several experimental compounds have emerged from this strategy.

5.1.1 Ligands Targeting Several Monoaminergic Receptors

A combination of chemical scaffolds responsible for interaction with 5-HT_6R/5-HT_7R and 5-HT_{2A}R/D_2R yielded a hybrid molecule **1**, which elicited favorable psychotropic effects (Fig. 11). In pharmacological studies, the selected multi-modal ligand **1** showed antidepressant and antipsychotic activity and did not affect cognition, in contrast to the eight antipsychotic drugs tested in the same experimental setting [199].

Similarly, a series of multi-modal ligands exhibiting high affinity to SERT, D_2R, 5-HT_{1A}R, 5-HT_6R, and 5-HT_7R have been identified (Fig. 11). It has been shown that tetrahydropyridin-4-yl-1*H*-indole is a privileged scaffold, which accounts for an interaction with SERT, D_2R and 5-HT_{1A}R, and its combination with the aryl sulfonamide moiety provides additional interaction with 5-HT_6R and 5-HT_7R. The selected compound **2** was tested in vivo and found to exhibit antipsychotic and antidepressant activity, as well as exert memory-enhancing effects [200].

Another notable approach of identifying novel MTLDs relies on combining D_2R partial agonism with 5-HT_6R antagonism. The partial D_2 agonism concept is based on the modulation of dopaminergic neurotransmission at a low sufficient level that simultaneously prevents the occurrence of extrapyramidal side effects by preventing excessive D_2R blockade in the striatum [201]. This strategy resulted in the development of a series of hybrid molecules, combining the 5-HT_6 and D_2 pharmacophores (Fig. 11). The selected molecule **3** displayed antidepressant and anxiolytic activity in aged animals, as well as promising procognitive effects [201]. The abovementioned compounds (**2** and **3**) are currently at an early stage of development by Adamed Pharma [202, 203].

5.1.2 Molecules Targeting Muscarinic M_1 and M_4 Receptors

Modulation of muscarinic receptors activity may improve both cognitive and psychosis-related symptoms. Targeting the centrally located M_1R and M_4R proved to enhance the memory function and reduce psychosis both in animal models and in clinics [204, 205]. Additionally, stimulation of muscarinic receptors controls the increase of amyloid-β levels and prevents memory impairments [206]. This evidence encouraged the development of dual ligands acting on M_1R/M_4R. Sosei Heptares, jointly with Allergan, is developing a series of dual M_1/M_4 agonists for the treatment of memory deficits and comorbid psychosis in patients with AD. The joint project has progressed to an advanced preclinical development stage [207]. Further data have not been revealed.

5.1.3 Cholinesterase and Monoamine Oxidase Inhibitor: Ladostigil

Degeneration of cholinergic cortical neurons is considered as a key pathology that accounts for the cognitive deficit in patients with AD. Drugs that act by inhibiting cholinesterase, and as a result, increasing cholinergic transmission in the affected cortical areas are expected to improve memory function. Interestingly, a cholinesterase inhibitor rasagiline reduced aggression and delusions in patients with AD [208].

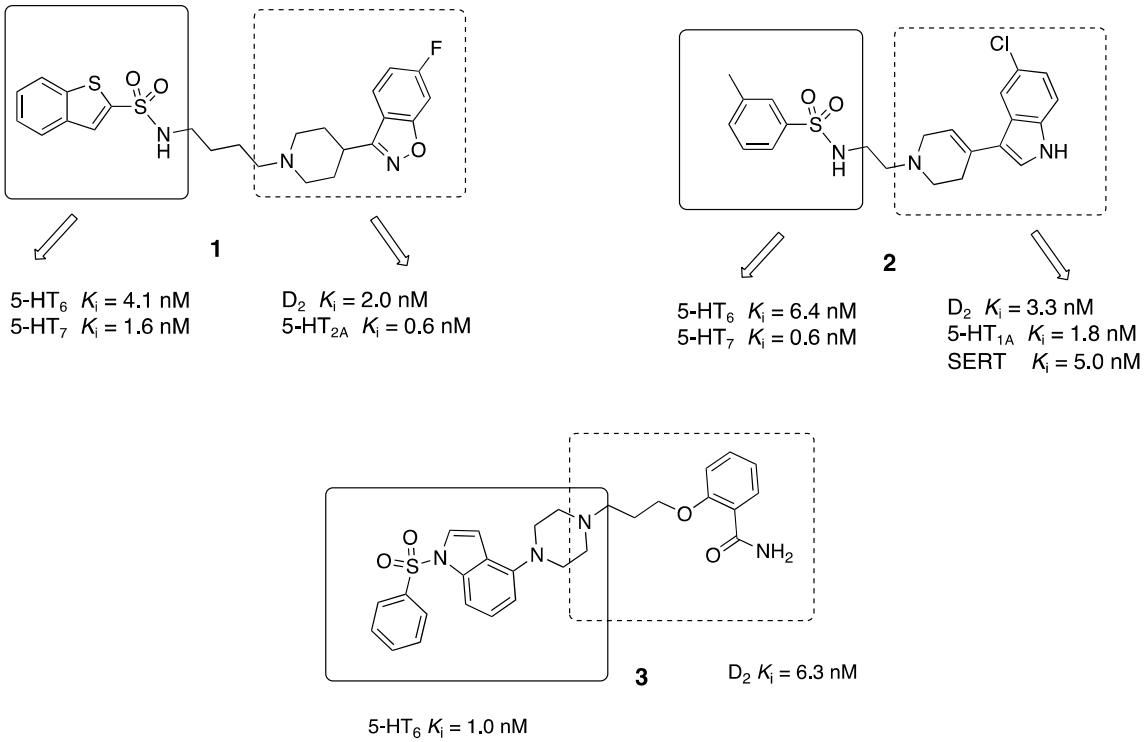


Fig. 11 Examples of multi-target-directed ligands obtained by combining the scaffolds responsible for interactions with 5-HT_6R, 5-HT_7R, 5-HT_{2A}R, and D_2R (discovery stage). *SERT* serotonin transporter

In a dual-acting drug, ladostigil, the carbamate fragment of rivastigmine, which accounts for the inhibition of cholinesterases, was merged with the *N*-(prop-2-yn-1-yl)-2,3-dihydro-1*H*-inden-1-amine fragment of rasagiline, which blocks the activity of monoamine oxidases A and B (Fig. 12) [209]. Ladostigil is a multi-modal agent developed by Avraham Pharmaceuticals to treat patients with mild cognitive impairment with concomitant behavioral symptoms. Preclinical studies showed that ladostigil improves memory deficits and exerts anxiolytic and antidepressant-like activity [210, 211]. Therefore, ladostigil has been suggested for use in patients with dementia with comorbid depression; however, no clinical data are available so far [210].

5.1.4 Ligands Targeting Serotonin 5-HT_6 and 5-HT_{2A} Receptors

Serotonin 5-HT_6 receptors are localized in the cortical and limbic areas, and ligands modulating the activity of 5-HT_6 receptors exert memory-enhancing, anxiolytic, and antidepressant effects [47, 48]. Importantly, several selective 5-HT_6 antagonists entered clinical trials and have been regarded as potential drug candidates for the treatment of cognitive impairment associated with AD [48, 212].

Similarly, serotonin 5-HT_{2A} receptor has emerged as a promising target for the treatment of AD, owing to its strong relationship with the pathology of dementia-related psychosis (see Sect. 2). Therefore, merging 5-HT_{2A}R and 5-HT_6R into a single chemical entity, having the pharmacological activities of both the receptors, may be beneficial in the treatment of dementia-related psychosis. Small molecules targeting 5-HT_6R and 5-HT_{2A}R are currently under development (discovery phase/advanced preclinical development stage) for the treatment of dementia-related psychosis by Adamed Pharma [213]. The chemical structure and preclinical data have not been disclosed.

6 Safety Issues Regarding Pharmacotherapy of Dementia-Related Psychosis and Agitation/Aggression: Summary of Off Targets

Previous studies indicated that patients with dementia were found to be particularly sensitive to side effects induced by atypical antipsychotics [214]. Patients with dementia seem to be at a greater risk of developing antipsychotic-associated stroke events [215]. It should be emphasized that atypical antipsychotics used so far in clinical settings (risperidone, olanzapine, quetiapine, and aripiprazole) interact with multiple receptors, including "off targets," which induce serious side effects (Table 4). For instance, similar to the first

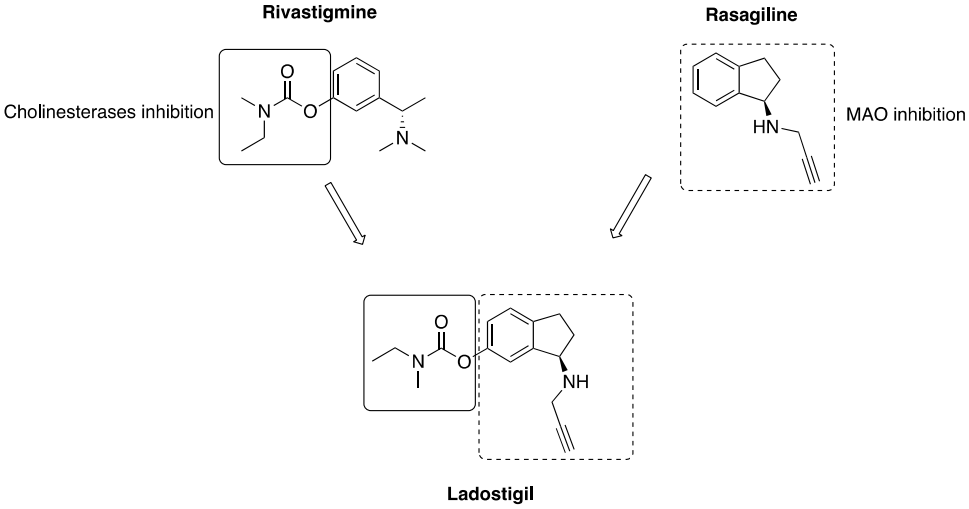


Fig. 12 Chemical structure of ladostigil. Ladostigil is composed of two fragments: the carbamate moiety of rivastigmine, which accounts for the inhibition of cholinesterases, merged with the *N*-(prop-2-yn-1-yl)-2,3-dihydro-1*H*-inden-1-amine fragment of rasagiline, which blocks the monoamine oxidases (MAO) A and B [209]

generation of antihistamines, antipsychotic agents tend to induce excessive daytime sleepiness owing to their high affinity to H_1R present in the brain [216]. Interaction with alpha-adrenoceptors (risperidone and quetiapine) causes orthostatic hypotension, and as a result, may increase the risk of falls and hip fractures [217]. Moreover, a large clinical study found a correlation between the increased risk of stroke and treatment with antipsychotics that exhibit high binding affinity to alpha-2 adrenoceptor and M_1R. A possible mechanism underlying this relationship is that blockade of alpha-2 adrenoceptor and M_1 may induce orthostatic hypotension and tachycardia, which prompts unstable hemodynamic conditions and increases the risk of stroke [214, 215]. In addition, blockade of the muscarinic receptors intensifies the cholinergic deficit and worsens cognitive functioning in patients with dementia, who already have memory impairment. Blockade of M_1R may induce additional uncomfortable symptoms, such as severe constipation and urine retention [218]. Furthermore, previous studies showed that inhibition of hERG (human ether-a-go–go-related gene) potassium channel has been considered as the most common mechanism of drug-induced cardiotoxicity (prolongation of QT interval). Therefore, evaluation of the potential inhibitory effects on the hERG channel should become an obligatory safety practice in the early stages of drug discovery for dementia-related psychosis and agitation/aggression [219, 220].

Considering the safety issues regarding elderly patients and their particular sensitiveness to adverse reactions, future therapeutic agents designed for dementia-related psychosis and agitation/aggression should not antagonize the muscarinic, adrenergic, and histaminergic receptors or the hERG channel [112].

Table 4 Simplified representation of an off-target receptor profile

Receptor	Pharmacological activity
Side-effect receptor action	
5-HT_{2C}	Weight gain
Alpha-2	Orthostatic hypotension
H_1	Excessive sedation, weight gain
M_1	Memory deficits, anticholinergic side effect
hERG channel	QT prolongation, arrhythmia

hERG human ether-a-go–go-related gene

7 Conclusions and Future Perspectives

Treatments currently used for dementia-related psychosis and agitation/aggression pose a great challenge to clinicians, and specifically targeted pharmacotherapies are lacking. Despite known harms and modest clinical efficacy, antipsychotics still are often administered off-label to control some symptoms [221]. Several clinical experts have agreed that to optimize the clinical response, patients with dementia should be treated with specifically developed medications that interact with pharmacologically relevant targets [16, 222, 223]. Within this context, preclinical and clinical studies have pointed out various biological targets that might constitute potential therapeutics for dementia-related psychosis and agitation/aggression.

Considering that the polymorphism of serotonin $5\text{-HT}_{2A}R$ and its disrupted functioning has been associated with the onset of psychosis and aggression in AD, it seems justifiable that the ligands modulating the activity of $5\text{-HT}_{2A}R$ could be attractive therapeutic agents for dementia-related psychosis and aggression [26, 27, 82]. A selective inverse agonist of $5\text{-HT}_{2A}R$ (pimavanserin) and novel atypical antipsychotics acting as 5-HT_{2A} antagonists (lumateperone, brexpiprazole) have advanced to phase III clinical trials after

showing promising efficacy in phase II studies in the management of dementia-related psychosis and agitation [58, 73, 114]. A phase III study has reported promising results for brexpiprazole, which significantly reduced agitation in patients with dementia, and its long-term efficacy will be further evaluated in a treatment-extension study [114]. In contrast, a phase III clinical trial that investigated the efficacy of lumateperone in reducing dementia-related agitation has been terminated because of a lack of efficacy [119]. Moreover, several compounds targeting 5-HT_{2A}R are in the early stage of the drug discovery process [199, 213]. In addition, the role of 5-HT_{1A}R is well elucidated in the onset of neuropsychiatric symptoms [34]. A 5-HT_{1A}R/5-HT_{1B}R agonist eltoprazine has also completed phase II clinical trials, showing positive results in suppressing AD-related aggression. Similarly, pathological changes in the function of alpha-1 adrenoceptor have been linked with the onset of aggressive behavior in patients with AD [148]. A centrally acting alpha-1 adrenergic antagonist prazosin is currently being investigated in a phase II study in the treatment of dementia-related aggression.

Several groups of patients with dementia with comorbid conditions may require specific adjusted pharmacological treatment. The episodes of nocturnal agitation in patients with dementia seem to require an agent displaying sedative properties and adjunctive sleep-promoting activity [174]. Within this context, two generic drugs, mirtazapine and gabapentin, are currently being investigated in phase III and phase IV trials, respectively. Both agents exhibit sedative properties and the ability to improve sleep quality, which may be suitable for this subgroup of patients.

Molecules acting via the inhibition of SERT appear to constitute another class of promising therapeutics [32, 33]. Polymorphism of the SERT has been associated with AD-related aggression. Significant clinical efficacy of a selective SERT inhibitor, citalopram, has been observed in a phase III clinical trial. However, citalopram induced cardiac side effects, and therefore, its long-term clinical application remains dubious. Currently, a phase III clinical trial is recruiting patients to evaluate the safety and efficacy of the *S*-enantiomer of citalopram, escitalopram, in reducing AD-related aggression. Escitalopram seems to be a safer alternative and does not tend to induce risky cardiac reactions [106]. It is worth nothing that dextromethorphan displays high affinity to SERT, which further supports the evaluation of its combined formulations (AVP-786 and AXS-05) in clinical trials. Both formulations are currently being investigated in ongoing phase III studies. The interim analysis of the study with AXS-05 showed promising outcomes and reported no safety issues [63].

Although certain drug candidates presented here act on the molecular targets that do not meticulously match the pathology of dementia-related psychosis and agitation/aggression, their promising pharmacological profile suggests their potential therapeutic utility. Favorable pharmacological properties have been reported for mGluR2, CB_1, NMDA, M_4, and M_1/M_4 agonists. A CB_1R agonist, nabilone, showed efficacy in reducing aggression in patients with dementia in a recently completed phase II/III clinical trial. An mGluR2 agonist, LY2979165, has advanced to phase II clinical trials that will investigate its safety and efficacy in the treatment of dementia-related psychosis and agitation/aggression. Similarly, an indirect NMDA agonist compound SND-51 has advanced to phase II clinical trials that will evaluate its efficacy in the treatment of dementia and psychosis. A selective M_4 receptor agonist, HTL0016878, has progressed to phase I clinical trials. In addition, various compounds acting on the pharmacologically relevant targets (5-HT_6R and M_1R/M_4R) have progressed to an advanced preclinical development stage. To sum up, future drugs targeting mGluR, NMDA receptors, CB_1R, M_1/M_4R, and 5-HT_6R also offer the possibility to tackle dementia-related psychosis and agitation/aggression.

Additionally, the key success of a clinically effective agent will likely depend on its safety and lack of harmful side effects [8, 9, 11]. Considering that previous clinical observations have shown that patients with dementia are at a higher risk of stroke [112], future drug candidates for patients with dementia should consistently avoid interactions and further blockade of alpha-2 adrenoceptors, M_1R, H_1R, and the hERG channel to avoid cardiotoxicity, stroke, excessive sedation, and memory impairments.

Nevertheless, the future pharmacotherapy of dementia-related psychosis, agitation/aggression will likely depend on the successful compilation of phase III clinical trials and further approvals. So far, the most promising results have been observed for compounds modulating serotoninergic signaling. Another set of molecules displaying favorable pharmacological activity are at an early stage of development.

Compliance with Ethical Standards

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